

Modern Concepts of Cardiovascular Disease

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ESSENTIAL HYPERTENSION — PART I

Hypertension, as it occurs in man, is not a disease entity nor even a uniform syndrome with consistent symptomatology and course. On the contrary, elevation of arterial pressure is merely a clinical sign which occurs in a large number of diseases and may be produced by one of several mechanisms. Thus when hypertension is found the clinician is faced immediately with the important problem of discovering as soon as possible by careful history, physical examination and intensive special study whether the elevated arterial pressure (a) is merely a secondary result of another and underlying disease, (b) is due to a remediable renal lesion or (c) is truly a hypertension of unknown etiology.

Essential hypertension as a diagnosis refers to an abnormally high systolic and diastolic arterial pressure occurring in individuals who do not have inflammatory kidney disease, urinary tract obstruction or other disorders which are known to result in elevation of the blood pressure. It is really a diagnosis arrived at by exclusion of other conditions.

Pathogenesis: Certain rules apply to the pathogenesis of all types of hypertension, whatever their cause or course. An elevation of arterial blood pressure might conceivably be due to (1) increased blood volume, (2) increased viscosity of the blood, (3) increased cardiac output, (4) increased peripheral resistance by arteriolar constriction or (5) any combination of these four factors. In addition, cardiac output and peripheral resistance are controlled partly by the sympathetic nervous system and partly by circulating hormones, so that changes in these two factors are susceptible of still further analysis. Essential hypertension has been studied more completely in this respect than have other types of hypertension.

Cardiac output, blood volume and blood viscosity having been found normal, it became obvious that increased peripheral resistance must be the important abnormality. Because physiologists, beginning with Ludwig, had demonstrated that constriction of the splanchnic vessels can elevate systemic blood pressure conspicuously, the favorite earlier hypothesis held that the major abnormality in the hypertensive individual consisted of an increase in peripheral resistance due to increased tone of the splanchnic arterioles particularly.

However, if vasoconstriction were limited to the splanchnic vessels it would be expected that the resulting hypertension should increase the flow of blood to other regions such as skin and muscle where, according to this hypothesis, arteriolar tone is still normal. Yet it was found that blood flow in the extremities and, by indirect methods, in brain tissue is generally within normal limits. The figures, with few exceptions, offer little or no evidence for selective and excessive constriction in the splanchnic area, but suggest rather a slight and widespread increase of arteriolar tone throughout the whole vascular system.

Despite this increase in basic tone the arterioles still respond approximately normally to local heat, local cold, metabolites, epinephrine, pituitrin, histamine, tyramine, body warming and body chilling. Some sensory stimuli, e.g. noise, pinching and deep breathing, produce in hypertensive individuals a vasoconstriction which is qualitatively and quantitatively similar to that occurring in normal subjects.

These observations provide a rational explanation for the insidious onset of hypertension in most instances, and for the frequency with which it is discovered by accident. These patients do not suffer from diminished blood flow, nor is there gross evidence of significant ischemia of vital organs until

structural changes develop in their arteries or arterioles. Despite well established hypertension we frequently find that the kidneys are performing their excretory functions normally as measured by rough clinical methods such as a concentration test, phenol-sulphonphthalein elimination, or urea clearance. With more refined tests by inulin and diodrast clearances, Smith and his coworkers have concluded that the efferent arterioles in the kidneys are constricted, and that renal blood flow is reduced, but that the volume of glomerular filtrate is nevertheless maintained at its usual level because the blood pressure, and therefore the filtration pressure, in the glomerular capillaries is increased. The results indicate that, of the various tissues studied so far in hypertension, kidney tissue is more likely than others to have an abnormally low flow and that renal blood flow diminishes prior to, rather than with, the destruction of the renal parenchyma. In the extremities, on the contrary, arteriolar tone and blood pressure are increased more nearly in proportion so that blood flow remains approximately normal until cardiac failure or vascular sclerosis supervenes.

This generalized increase in arteriolar tone throughout the body might be either neurogenic or humoral in origin. The evidence obtained in experimental hypertension produced in animals by Goldblatt is overwhelmingly against the existence of overactivity of the sympathetic nervous system. Total sympathectomy neither prevents the development of hypertension in animals nor reduces hypertension induced previously. In essential hypertension of man the evidence is less clear. When sympathetic vasoconstrictor impulses to the extremities of hypertensive and normal individuals are blocked by local anesthesia, or caused to disappear by reflex vasodilatation, blood flow increases about equally in both, indicating that the sympathetic nervous system is not overactive. Yet in selected patients sympathectomies have been followed by lowering of blood pressure and also by regression of certain symptoms and signs of hypertension.

The evidence for a humoral mechanism is more varied and suggestive but still not complete. Transplantation of an "ischemic" kidney into the neck of a nephrectomized dog elevates the blood pressure, while complete ligation or removal of an "ischemic" kidney from a hypertensive dog reduces blood pressure. In man, hypertension has been reduced by the surgical removal of a single kidney injured by pyelonephritis, hydronephrosis, or congenital anomaly usually affecting the circulation. A diseased kidney may therefore produce in man a "renal hypertension" analogous to that which Goldblatt produces in animals by reducing the lumen of the renal artery.

The search for a pressor substance in the blood of patients with hypertension has been intensive at intervals for many decades. Epinephrine, pituitrin, tyramine and guanidine have all been referred to as the responsible agents at various times in the past but their concentrations in the circulating blood have not been consistently elevated in hypertension and sporadic studies claiming increased vascular sensitivity to certain of these compounds have not been confirmed. None of them produce the generalized and accurately balanced increase of blood pressure and peripheral resistance which is required if peripheral blood flow is to remain approximately normal despite hypertension. These substances produce a profound peripheral vasoconstriction and reduce blood flow in the skin, while hypertensive patients and animals retain a normal cutaneous circulation.

In 1898 Tigerstedt and v. Bergmann observed that

saline extracts of kidney tissue, while sometimes toxic, usually produced a slowly developing rise of blood pressure persisting for 30 to 45 minutes after injection intravenously. In striking contrast to most other pressor substances the protein-like "renin" in these purified kidney extracts elevates blood pressure in experimental animals without reducing peripheral blood flow, matching to that extent the circulatory condition characteristic of clinical hypertension. The rise in blood pressure is temporary, however, and repeated injection leads to diminishing effect (tachyphylaxis). Page and Houssay found independently that "renin" is not itself pressor but on combination with a pseudoglobulin in blood plasma (renin activator, Page; hypertensin precursor or hypertensinogen, Houssay) produces a dialyzable constrictor substance (angiotonin, Page; hypertensin, Houssay), which is directly pressor when injected into animals and man. Recent evidence suggests also that from normal kidney tissue can be obtained a substance or substances of unknown composition and stability which destroy angiotonin and hypertensin.

In the past 40 years many workers have claimed that it is possible under certain circumstances to demonstrate in the blood plasma of hypertensive patients or animals unique constrictor activity whereas control plasma injected into the same test preparations is inert. It must be confessed, however, that while many methods have been suggested none has so far proved generally dependable in clinical work, and in none has there been proved any consistently quantitative relation between the height of blood pressure and the intensity of constriction induced in the assay preparation. Transfusions of blood from hypertensive donors into normal subjects have yielded equivocal results. Various prepared extracts from kidneys of hypertensive animals and patients are not uniformly more pressor than similar extracts of normal kidneys, though average results sometimes suggest a greater renin content.

Another hypothesis suggests that the pressor material responsible for hypertension is one or more of the pressor amines, which might be released when ischemia interferes with the action of enzymes such as decarboxylase and particularly amine oxidase which have been found in kidney tissue. These enzymes, acting for example on di-hydroxyphenylalanine in the presence of oxygen, produce di-hydroxyphenylacetic acid, an inert substance, whereas in the absence of oxygen hydroxytyramine, a pressor substance, appears instead. Again, demonstration of amines in the blood of hypertensive patients has been claimed, but not so far verified by wide testing. It must also be recalled that while tyramine elevates blood pressure it does not duplicate the hypertensive state so exactly as renin. The renin and amine hypotheses are both of theoretical interest because they (a) attempt to explain the "humoral" factor in hypertension and (b) form the basis of two efforts to devise a "specific" treatment of hypertension, both being still in the experimental stage.

Despite the evidence in favor of the humoral concept and despite the inability to demonstrate abnormal activity of the autonomic nervous system, it must be emphasized that vasoconstriction of the neurogenic type is superimposed periodically upon the high basal arteriolar tone characteristic of hypertension, just as is the case in the transient physiological elevations of blood pressure in normal individuals. Clinically it is agreed that significant reduction of pressure occurs in many hypertensive patients during mental and physical rest. Blood pressure can be reduced abruptly, though not quite to normal levels, by compression of the carotid sinus so that the moderator mechanism is apparently intact, though overpowered by a more potent agent. The frequent association of essential hypertension with continued nervous tension, emotional stress and anxiety, indicates also that even though the fundamental abnormality be humoral in origin, the sympathetic nervous system can still accentuate the grade of hypertension and accelerate its advance.

Moreover, constitutional susceptibility and heredity seem to play a significant role in many instances.

A history of hypertension occurring early in life in a patient's parents or siblings is found in some cases of the malignant form of essential hypertension. The children of hypertensive patients often react with an exaggerated rise of pressure when one hand is immersed in cold water. These "hyper-reactors" appear to be more likely to develop hypertension in later life than are those who react normally. Given an equal amount of organic renal disease, as in polycystic kidney disease or pyelonephritis, hypertension appears in some individuals and not in others. These variations may be due to unrecognized differences in the details of structural damage, to an hereditary defect or to early environmental changes but in any case illustrate the highly variable response of the vascular system to types and grades of renal pathology which seem similar by present methods of examination.

Pathology: In a few well studied cases persistent hypertension has existed for years and, death having been caused by another condition, autopsy has revealed no significant pathology of the renal arterioles. The nearest approach to a comprehensive *in vivo* study of this type in man is a very recent one by Castleman and Smithwick. In renal biopsies from 100 patients subjected to sympathectomy for treatment of hypertension it was found that in 53 the organic renal vascular disease was so slight that it seemed unlikely that this cause alone could have reduced renal blood flow sufficiently to make this one factor solely responsible for the hypertension. If these biopsies represent accurately the state of the entire vascular bed of both kidneys, it seems likely that the degenerative lesions seen after death are secondary to hypertension and not its cause. Attention must once more then be focused upon simple arteriolar spasm as the initial inciting agent in man, which may begin the same cycle produced by clamping the renal artery which Goldblatt has used so successfully to produce hypertension in animals.

After death from long-continued effects of chronic essential hypertension, however, organic vascular disease in the kidneys is found in practically every instance (Moritz and Oldt). In benign nephrosclerosis death from renal insufficiency and uremia is rare, and pathologists find less striking renal changes. Patients with the malignant form of essential hypertension are much more apt to die in uremia and then subcapsular hemorrhages, necrosis of afferent arterioles and gross destruction of glomeruli are almost always found at autopsy. The earlier tendency to regard benign and malignant arteriolar nephrosclerosis as separate diseases is less tenable since Goldblatt has shown experimentally that animals will develop a benign or a malignant form of hypertension and corresponding arteriolar disease depending upon whether renal ischemia and renal insufficiency are mild or severe respectively. Clinicians are therefore justified in speaking of the benign phase, or malignant phase, of essential hypertension particularly since occasional patients will exhibit fairly clear transitions from a benign to a malignant course; and at autopsy the pathologist may find organic changes characteristic of both conditions.

The relative importance of slight but definite unilateral abnormalities of the renal pelvis, vessels or ureters has been explored during life in hypertensive patients by urography, both intravenous and retrograde. In autopsies sclerosis and partial thrombosis of the renal arteries are found rather frequently. Even though true "renal" hypertension, in the sense of being curable by unilateral nephrectomy, is relatively rare, it still occurs frequently enough to make it obligatory to exclude the possibility of gross unilateral disease in every case of hypertension not otherwise explained.

Finally, any hypertension whatever its cause increases the work of the heart, induces hypertrophy and predisposes to failure. The arterioles and arteries become sclerotic and subject to thrombosis or hemorrhage. The vessels of the spleen, pancreas, coronary system and brain all may be involved to different degrees. The varying symptomatology of hypertension in its later stages reflects the focal and unequal distribution of these sclerotic changes.

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